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Highlight Review

Ring-Expanding and Ring-Opening Transformations of Benzofurans and Indoles with Introducing Heteroatoms

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Abstract

Skeletal transformations of heteroaromatic compounds with cleaving their endocyclic bonds have been emerging as new synthetic tools in modern organic chemistry. Especially, endocyclic insertion of a heteroatom into a heteroaromatic core is a game-changing approach to exotic classes of heterocyclic compounds. In this Highlight Review is summarized recent progress of ring-expanding and ring-opening reactions of benzofurans and indoles.

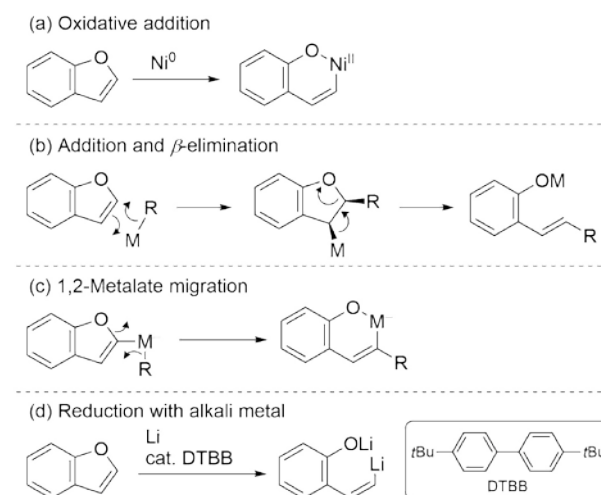
Introduction

Heteroaromatic compounds are highly important due to their wide variety and availability, and heteroaromatic cores are often included in functional materials or medicines. Therefore, a huge number of reactions to synthesize and functionalize heteroarenes have been reported. However, transformations of heteroaromatic cores with cleaving endocyclic carbon–heteroatom bonds are still limited despite great progress of organic synthesis. The infancy of such endocyclic transformations is naturally ascribed to large bond energies of C–O, C–N, and C–S bonds and decisive aromatic stabilization. If one can use heteroaromatic cores as building blocks through endocyclic transformations, novel and useful synthetic approaches would be provided.

In recent years, we have been interested in transformations of heteroaromatic compounds into other skeletons through partial disassembly of their cyclic structures, which we have coined ‘aromatic metamorphosis’.^{1,2} Previously our group achieved transformations of dibenzothiophenes,³ dibenzofurans,⁴ benzofurans,^{5–7} and indoles.⁸ To establish aromatic metamorphosis as a truly useful strategy in organic synthesis, we need to understand the reactivity of each heteroaromatic rings.

Benzofuran, a singly benzo-fused furan, is distinct from furan and dibenzofuran in that the 2,3-position in benzofuran can be regarded as (Z)-styryl phenyl ether of reasonable reactivity. Therefore, several approaches using the special reactivity of the vinyl ether are conceivable to transform the furan ring in benzofuran. We can categorize the reported cleavages of C2–O bonds of benzofurans via organometallic species into the following four types on the basis of reaction mechanisms: (a) oxidative addition; (b) addition followed by β -

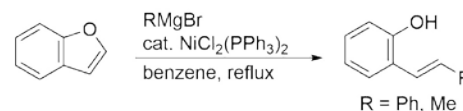
elimination; (c) 1,2-metalate migration; and (d) reduction with alkali metal (Scheme 1).



Scheme 1. Ring-opening reactions of benzofuran categorized by reaction mechanism.

(a) Oxidative addition

Ni-catalyzed C–O bond cleavages are generally considered to proceed via oxidative addition due to the high electron density of Ni(0) species (Scheme 1a).⁹ In 1979, Wenkert reported ring-opening arylation and alkylation of benzofuran with the aid of a nickel catalyst and Grignard reagents to afford stilbene derivatives (Scheme 2).^{9a} This reaction is not only the first example of catalytic ring-opening transformations of benzofuran but also the earliest work of catalytic C–O bond activations.¹⁰

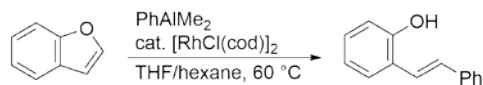


Scheme 2. Ni-catalyzed ring-opening arylation and alkylation of benzofuran.

(b) Addition and β -elimination

Fe and Rh catalysts can promote addition of organometallic reagents to the vinyl ether unit of benzofuran

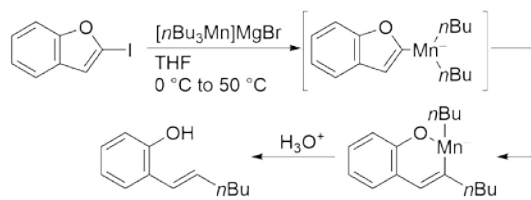
and subsequent β -elimination (Scheme 1b).¹¹ For example, ring-opening arylation of benzofuran with an organoaluminum reagent takes place in the presence of a Rh catalyst (Scheme 3).^{11b} As well as catalytic systems, Zr complexes react stoichiometrically with benzofuran to give the ring-opening products in a similar manner.¹² Besides alkylations and arylations, Cu-catalyzed cascade reaction composed of reductive ring-opening and the following hydroamination was also reported.¹³



Scheme 3. Rh-catalyzed ring-opening arylation of benzofuran with PhAlMe_2 .

(c) 1,2-Metalate migration

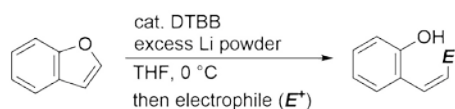
1,2-Migration in metalate complexes of 2-benzofurylmetal with other alkyl or aryl anions results in formation of the corresponding 6-membered 1,2-oxametallacycles (Scheme 1c).¹⁴ For instance, treatment of 2-iodobenzofuran with a manganate complex prepared from MnCl_2 and 3 equivalents of $n\text{BuMgBr}$ gives the butylation product with ring-opening of the furan moiety (Scheme 4).^{14b}



Scheme 4. Migratory ring-opening of benzofuran with a Mn ate-complex.

(d) Reduction with alkali metal

As another approach to ring-opening of benzofurans, reductive cleavage of the C2–O bond without transition metal catalysts is known (Scheme 1d). Treatment of lithium metal with benzofuran in the presence of an electron transfer catalyst results in selective cleavage of the C2–O bond to afford α -hydroxystyrene after acidic workup (Scheme 5).¹⁵ By employing other electrophiles instead of protonolysis, a series of substituents could be installed at the β -position of the styrene skeleton.



Scheme 5. Reductive ring-opening of benzofuran with Li powder followed by electrophilic trapping.

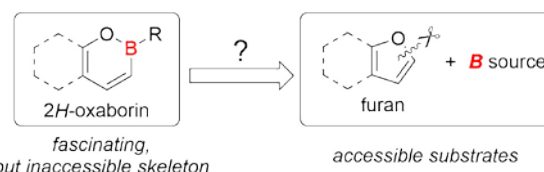
All of these aforementioned ring-opening transformations of benzofurans had been limited to ending up with C–C bond formation and reduction. Introducing heteroatoms to benzofuran with cleaving its endocyclic bond had never been achieved, while Yus reported a formal insertion of a C=O moiety to the C2–O bond of benzofuran.¹⁵ Moreover, a skeletal transformation of an indole core with C–N bond cleavage is extremely difficult due to the strong aromaticity of indole although it has a structure similar to benzofuran. Ring-

opening or ring-expanding transformations of indoles are reported as very limited examples^{16,17} in contrast with benzofurans.

This Highlight Review deals with our recent research for skeletal transformations of benzofurans and indoles with introducing heteroatoms, with categorizing their reaction mechanisms.

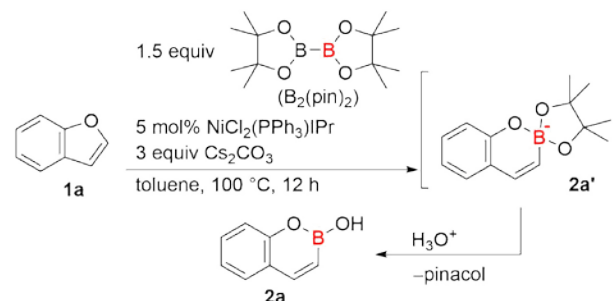
Ni-Catalyzed Boron Insertion into Benzofurans

Boron-containing heterocycles, called ‘boracycles’, have been attracting surging attention in this century. Because the vacant p -orbital on a boron atom affects π -conjugated systems, boracycles show unique properties. Recently, 2H-oxaborins¹⁸ have emerged as functional molecules such as fluorophores, materials for optoelectronics,¹⁹ and synthetic intermediates.²⁰ However, despite the great importance of oxaborins, classical approaches to construct oxaborin skeletons are very limited. For example, very reactive boron halides or complicated boron compounds are required as reagents or substrates.²¹ If a boron atom can be directly inserted into a furan ring, it should be a useful and straightforward synthetic approach to an oxaborin skeleton (Scheme 6).



Scheme 6. Working hypothesis for constructing oxaborin skeleton from furan core.

Finally, we revealed that the combination of a nickel catalyst and a diboron reagent can introduce a boron atom into benzofuran with cleaving the C2–O bond (Scheme 7).⁵ This reaction is the first example of catalytic introductions of a heteroatom into a heteroaromatic core. Surprisingly, the boron insertion product **2a** was stable under air and acidic conditions, and they could be purified on silica gel even with an eluent containing acetic acid.

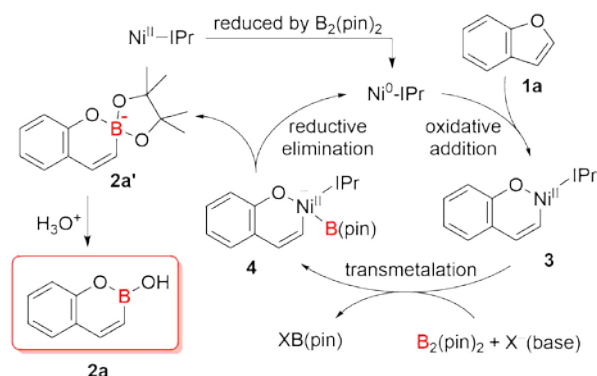


Scheme 7. Ni-catalyzed boron insertion into benzofuran

A plausible reaction mechanism of the boron insertion is described in Scheme 8. The C2–O bond of **1a** would undergo oxidative addition to a Ni(0) complex to give oxanickelacycle **3**. Transmetalation with $\text{B}_2(\text{pin})_2$ results in formation of borylnickel species **4** which affords **2a'** via reductive

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elimination with constructing a C–B bond. Before acidic workup of the reaction mixture, the product **2a'** exists as a precipitate in toluene and ^1H and ^{11}B NMR analysis in polar solvents supported the spirocyclic structure of **2a'**. Finally, treatment with aqueous HCl gives **2a**.

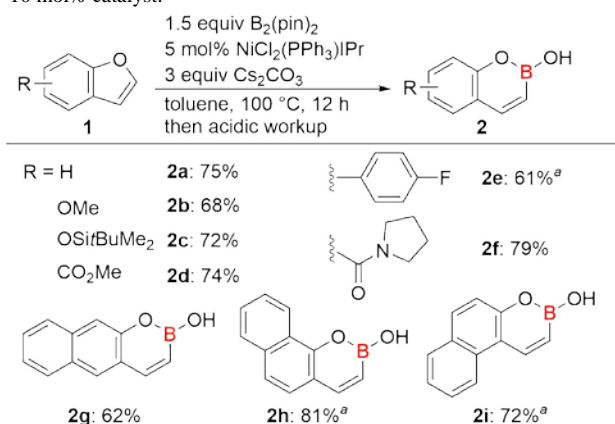


Scheme 8. A proposed mechanism of boron insertion into benzofuran.

Since the cleavage of the C2–O bond in this reaction proceeds via oxidative addition, Ni catalysts ligated with electron-rich phosphines or NHCs tended to be effective for the boron insertion, and $\text{NiCl}_2(\text{PPh}_3)(\text{IPr})$ complex (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) gave the best result. Although the diol moiety of diboron reagent does not remain in the product, only $\text{B}_2(\text{pin})_2$ gave **2a** in a good yield while other diborons bearing neopentyl glycol and catechol were totally ineffective for this boron insertion.

Notably, the boron insertion reaction had a good compatibility of functional groups (Table 1). For example, methoxy, siloxy, ester, and fluoro groups were compatible with this boron insertion, which would be potentially reactive in the presence of a Ni catalyst (**2b–2e**). As well as benzofurans, π -extended naphthofurans were also applicable to the boron insertion (**2g–2i**).

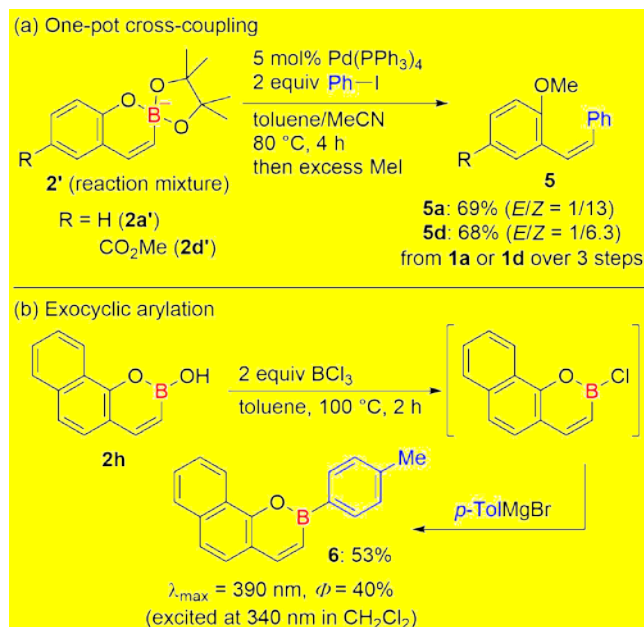
Table 1. Representative reaction scope of boron insertion of benzofurans.
^a10 mol% catalyst.



To prove the utility of the products as organoboron reagents, we performed several transformations of the resulting oxaborins. For example, Suzuki–Miyaura cross-coupling of borate intermediates **2a'** and **2d'** successfully took place in one pot with high stereoselectivity after etherification (Scheme 9a).

In these coupling reactions, acetonitrile as an additional solvent was important to increase the solubility of borate intermediates.

We also tried applying this boron insertion to the synthesis of a fluorescent molecule. *B*-aryloxaborins are also known as fluorophores and several dibenzoxaborins were synthesized to explore their photophysical properties.^{19a} We conducted introduction of an aryl ring onto the boron atom of naphthoxaborin **2h** to yield *B*-tolynaphthoxaborin **6**, which showed blue fluorescence with a quantum yield of 40% (Scheme 9b). DFT calculations of **6** revealed that the oxaborin core and the tolyl group on the boron atom are coplanar at the optimized structure, and the frontier orbitals of **6** are widely delocalized all over the π -system of **6**.



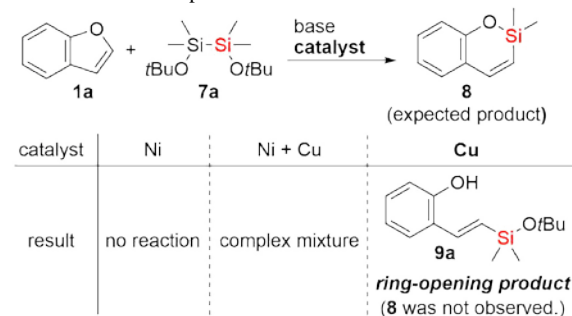
Scheme 9. Applications of the boron insertion products.

Cu-Catalyzed Ring-Opening Silylation of Benzofurans

Since catalytic boron insertion into benzofuran was established, we naturally aimed to expand this methodology to insertion of other heteroatoms. Considering the importance of organosilicon compounds as building blocks and functional materials in modern organic chemistry,²² we chose silicon as the next heteroatom for the insertion.

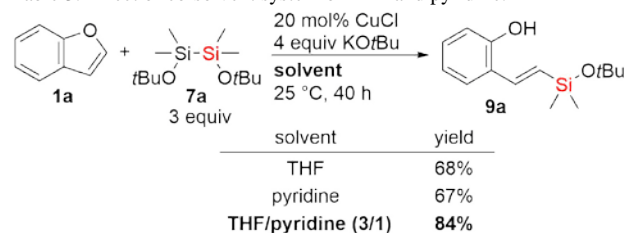
Initially we applied a disilane reagent instead of $\text{B}_2(\text{pin})_2$ to some Ni-catalyzed systems expecting formation of 6-membered oxasilacycle, oxasilin **8**.²³ However, benzofuran did not react at all and both benzofuran and the disilane were fully recovered (Table 2). Then a Ni/Cu co-catalysis was tested in order to promote transmetalation from disilane via silylcopper species, and a complex mixture was obtained without formation of oxasilin **8**. We thought Cu catalyst participated in ring-opening process of benzofuran, and then further condition screening with Cu catalysts was conducted. We eventually found that Cu-catalyzed ring-opening silylation of benzofuran with 1,2-di-*tert*-butoxy-1,1,2,2-tetramethyldisilane (**7a**)²⁴ took place instead of silicon insertion to form **8**.⁶

Table 2. Initial attempts for silicon insertion of benzofuran.



The effect of solvent is critical for this silylation of benzofuran. Only THF and pyridine gave the product in moderate yields (Table 3), while other ethereal solvents could not promote the reaction at all and amide solvents such as DMF and DMA resulted in decomposition of the product. Interestingly, a co-solvent system of THF and pyridine increased the yield of **9a**. Although the actual reasons of the improvement of reaction efficiency are not clear, addition of pyridine to THF might reduce the aggregation of silylcopper species in the reaction mixture to enhance the reactivity of silylcopper.

Table 3. Effect of co-solvent system of THF and pyridine.



Other silicon sources **7b–7e** were also tested for the silylation, and a *tert*-butoxy group on silicon atoms was found to be essential for successful silylation of benzofuran (Table 4). Although diethoxydisilane **7b** probably underwent ring-opening silylation, the product was decomposed under the reaction conditions since the steric hindrance around the ethoxysilyl group is insufficient. On the other hand, hexamethyldisilane (**7c**) did not react at all with **1a**. These results indicate that the Lewis acidity of the silicon atoms in **7** is important to activate a disilane with a base. While silylboranes are often used as silyl anion equivalents for many silylation reactions,²⁵ silylborane **7d** gave a complex mixture under the reaction conditions. Unsymmetrical disilane **7e** gave a mixture of two silylation products with no selectivity.

Substrate scope of the ring-opening silylation is shown in Table 5. Halogen atoms including chlorine endured reaction conditions (**9d** and **9e**). Benzofurans bearing a monocyclic furan or thiophene underwent silylation only at the benzofuran side (**9g** and **9h**). Attempted double silylation of naphthobifuran gave rise to mono-silylation only at the one side affording **9j–Me** after methylation. The exclusive mono-silylation is attributable to the negative charge on the phenoxy moiety emerging after the first ring-opening silylation that would prevent the intermediate from coordination to electron-rich silylcopper species.

Table 4. Screening of silicon sources for ring-opening silylation.

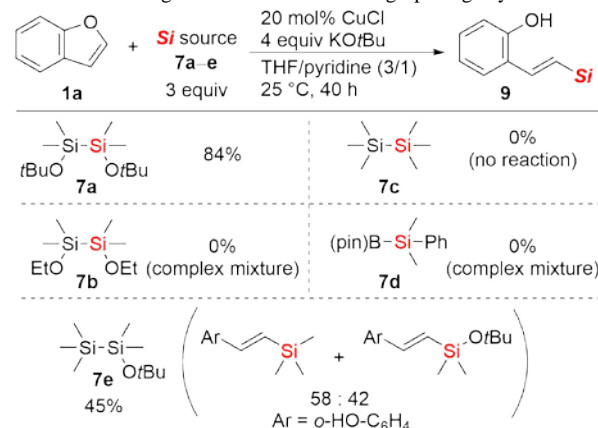
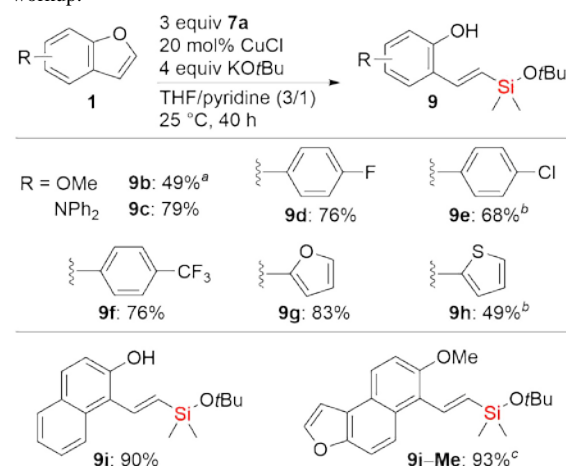


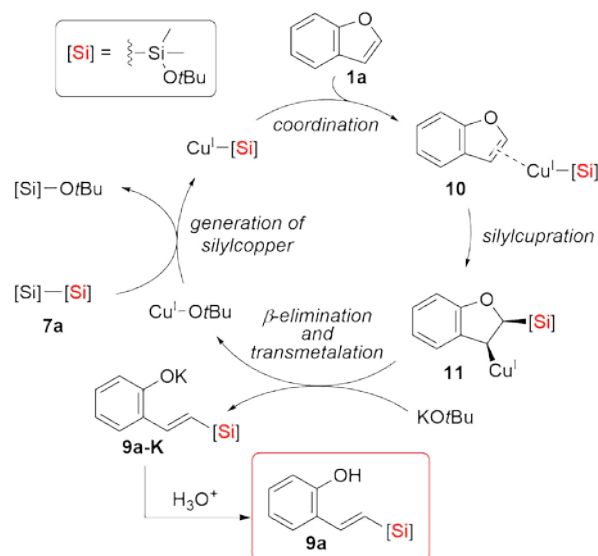
Table 5. Reaction scope of ring-opening silylation of benzofuran. ^a4 equiv **7a**, 5 equiv KOtBu. ^b30 mol% CuCl, 60 h. ^c25 equiv MeI was added before workup.



A plausible reaction mechanism for this silylation is described in Scheme 10. At the first step, CuOtBu should be generated from CuCl and KOtBu, and the formation of silylcopper species from the disilane **7a** and CuOtBu would then take place.²⁶ After coordination of **1a** to the Cu center, the complex **10** undergoes silylcupration to form **11**. The following β -elimination would furnish potassium β -(silylvinyl)phenoxide **9a–K**, and regeneration of silylcopper species from CuOtBu and **7a** would proceed. As a related work, Studer also reported ring-opening silylation of benzofurans and indoles with a silyllithium reagent via silyllithiation.¹⁷

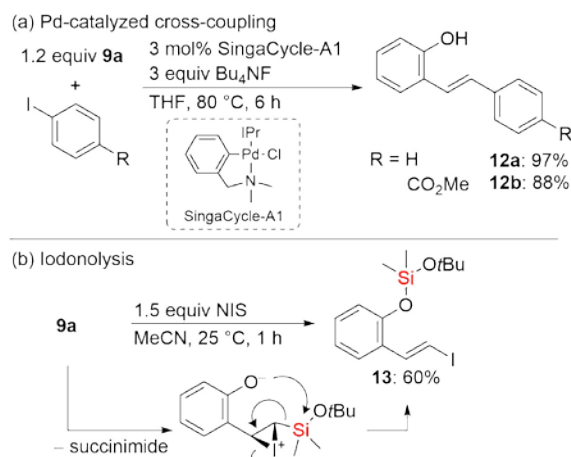
Computational studies were also performed to figure out the details of the reaction mechanism of this silylation. DFT calculations²⁷ suggested that the rate determining step would be the silylcupration (21.5 kcal mol⁻¹) and the following β -elimination would smoothly proceed (14.1 kcal mol⁻¹). These computational expectations also agreed with the experimental observations that 2-silyldihydrobenzofuran from **11** was not detected after acidic workup. In addition, β -elimination would proceed via *syn*-configuration to give the silylation product as an (*E*)-isomer.

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Scheme 10. A plausible reaction mechanism of ring-opening silylation of benzofuran.

We conducted transformations of a silylation product **9a**. Pd-catalyzed cross-coupling of **9a** with iodoarenes smoothly proceeded to furnish the corresponding (*E*)-stilbene derivatives **12a** and **12b** in good yields (Scheme 11a). Treatment of **9a** with NIS (*N*-iodosuccinimide) gave (*E*)-iodostyrene **13** with the hydroxy group protected by a silyl group via intramolecular silicon transfer (Scheme 11b).²⁸



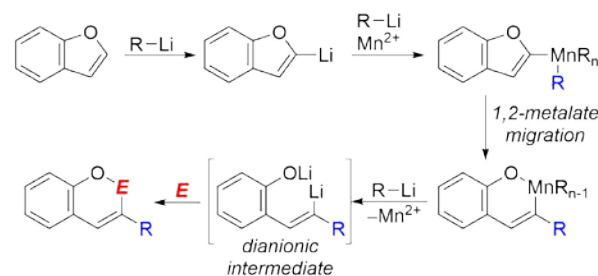
Scheme 11. Transformations of **9a**.

Heteroatom Insertion into Benzofurans with Divergency

Considering great interest in a series of oxaheterocycles including oxaborins and demands for efficiently providing them, diversity-oriented approaches from common intermediates would be ideal and robust to rapidly offer a variety of oxaheterocycles. With this in mind, we focused on Mn-mediated 1,2-metalate migration which affords a 'dianion' of an alkenylphenol from benzofuran (Scheme 4).^{14b} The dianionic species was expected to react with various electrophiles to furnish a series of 6-membered oxaheterocycles. This methodology composed of migratory ring-opening and trapping with a heteroatom electrophile could

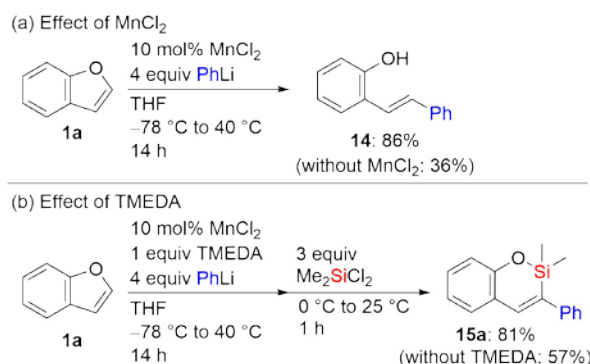
introduce both an aryl/alkyl group and a heteroatom to benzofuran skeleton in one pot, thereby increasing the diversity of oxaheterocyclic products efficiently.

The reported ring-opening of benzofuran with an alkylmanganese complex employed 2-iodobenzofuran as a substrate, which should be prepared from benzofuran.^{14b} To improve the availability of substrates, we used benzofuran without a substituent at the 2 position and employed a combination of an excess of an organolithium and a catalytic amount of MnCl₂. We expected that an organolithium would participate in deprotonation at the 2 position and a Mn catalyst would be regenerated via transmetalation between the oxamanganacycle and an organolithium (Scheme 12).



Scheme 12. Working hypothesis for divergent heteroatom insertion into benzofuran.

This catalytic system for the ring-opening process indeed worked well, and treatment of benzofuran with 4 equivalents of phenyllithium in the presence of 10 mol% MnCl₂ gave a stilbene derivative **14** in 86% yield (Scheme 13a). Although optimal conditions for ring-opening of benzofuran were in hand, the efficiency of trapping with an electrophile as the following step was unsatisfactory. To solve the problem, we tried a series of additives and finally we found that addition of 1 equivalent of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) increased the yield of silicon insertion product **15a** (Scheme 13b). TMEDA would help to reduce aggregation of dianionic species and thus enhance the reactivity of the intermediate to the electrophile.

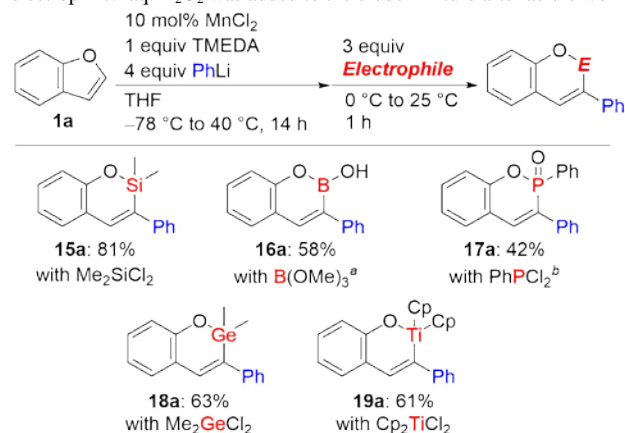


Scheme 13. Condition screening of ring-opening of benzofuran and electrophilic trapping of dianionic intermediate.

Next, a series of electrophiles were applied to this heteroatom insertion into benzofuran (Table 6). As well as silicon, other elements such as boron, phosphorus,²⁹ germanium, and titanium were successfully introduced to the cyclic structure by employing the corresponding electrophiles (**16a–19a**). Oxasilin **15a**, oxaphosphin **17a**, and oxagermin

18a showed blue fluorescence, and thus these skeletons are considered to be potentially usable for fluorophores. In addition, **18a** and **19a** were the first examples of syntheses of oxagermin and oxatitin cores, respectively. Although electrophilic trapping with Me_2SnCl_2 or Cp_2ZrCl_2 were likely to give the corresponding cyclic products according to ^1H NMR and MS analysis, they gradually decomposed during purification and could not be isolated in our hand.

Table 6. Diverse heteroatom insertion into benzofuran. ^a6 equiv electrophile. ^baq. H_2O_2 was added to the crude mixture after acidic workup.



As another advantage of this sequential heteroatom insertion, various substituents could be installed into the products by using other organolithium reagents or other benzofurans (Table 7). Not only (hetero)aryllithiums but also alkylolithiums were also applicable to this heteroatom insertion (**15g** and **15h**). Naphthofurans as well as benzofurans could be used for silicon insertion to afford the corresponding naphthoxasilins (**15l–15n**).

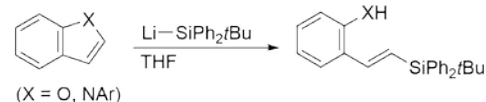
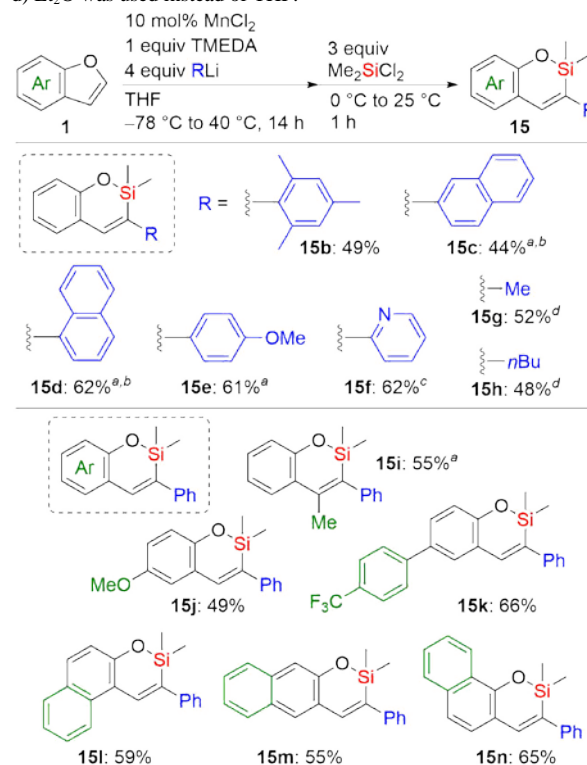
Lithium-Mediated Ring-Opening and Sequential Boron Insertion into Indoles

Azaborin cores have been attracting great attention for their aromatic system as well as functional materials and bioactive molecules.^{30–32} However, conventional synthetic methods for azaborins are not satisfactory because harsh conditions or complicated substrates are required, and thus skeletons or substituted substrates are required, and thus limited. If direct synthesis of azaborins from indoles, which is one of the most accessible heteroarenes, is achieved on the basis of our methodology of boron insertion, such a reaction should be a powerful method to expand new chemical spaces.

However, as described in the introduction, C–N bond cleavage of indoles is still one of the most challenging reactions in modern organic chemistry. This difficulty is derived from both the high aromaticity of the pyrrole core and the poorer leaving ability of R_2N^- anion than that of RO^- anion. Recently, Studer reported ring-opening silylation of benzofurans and indoles with the aid of silyllithium, which is the first example of ring-opening transformations of indoles (Scheme 14).¹⁷ This silylation is composed of silyllithiation and the following β -elimination which is shown in Scheme 1b.

Although this reaction proved indoles to undergo transformations with cleaving their C–N bonds, the compatibility of functional groups was insufficient due to the high reactivity of silyllithium.

Table 7. Reaction scope of silicon insertion into benzofurans. a) 20 mol% MnCl_2 . b) 2 equiv of TMEDA. c) $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$ for ring-opening step. d) Et_2O was used instead of THF.



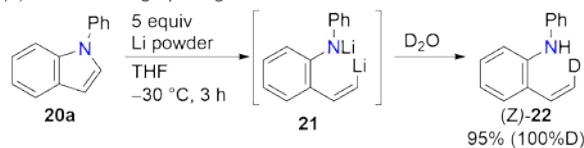
Scheme 14. Ring-opening silylation of benzofurans and indoles with a silyllithium reagent reported by Studer.

Many attempts were made in our group to cleave C2–N bond of indoles catalytically, but all of them failed. Next, we tried reductive ring-opening of indoles using alkali metal followed by trapping with electrophiles. Finally we found that treatment of Li powder with *N*-phenylindole (**20a**) successfully gave the ring-opening product (*Z*)-**22** after quenching with D_2O (Scheme 15a). This result also indicated the dianionic intermediate **21** existed in the reaction mixture with stereoretention. Although the optimized reaction conditions were similar to those of Yus's reductive ring-opening of benzofuran (Scheme 5),¹⁵ an electron transfer catalyst, 4,4'-di-*tert*-butylbiphenyl (DTBB), was not required in our system. Moreover, addition of phenylboronic acid pinacol ester ($\text{PhB}(\text{pin})$) as an electrophile to the reaction mixture after filtration furnished azaborin **20aa** in a good yield (Scheme 15b).⁸ Notably, the filtration was an important operation to obtain the product because the residual Li metal caused decomposition of the resulting azaborin. The use of

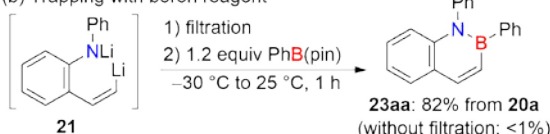
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organoboronic acid esters should be a great advantage over the conventional azaborin syntheses because various organoboronic acid esters are commercially available and easily handled.

(a) Reductive ring-opening of indole



(b) Trapping with boron reagent



Scheme 15. Reductive ring-opening of indole **20a** and electrophilic trapping of intermediate **21**.

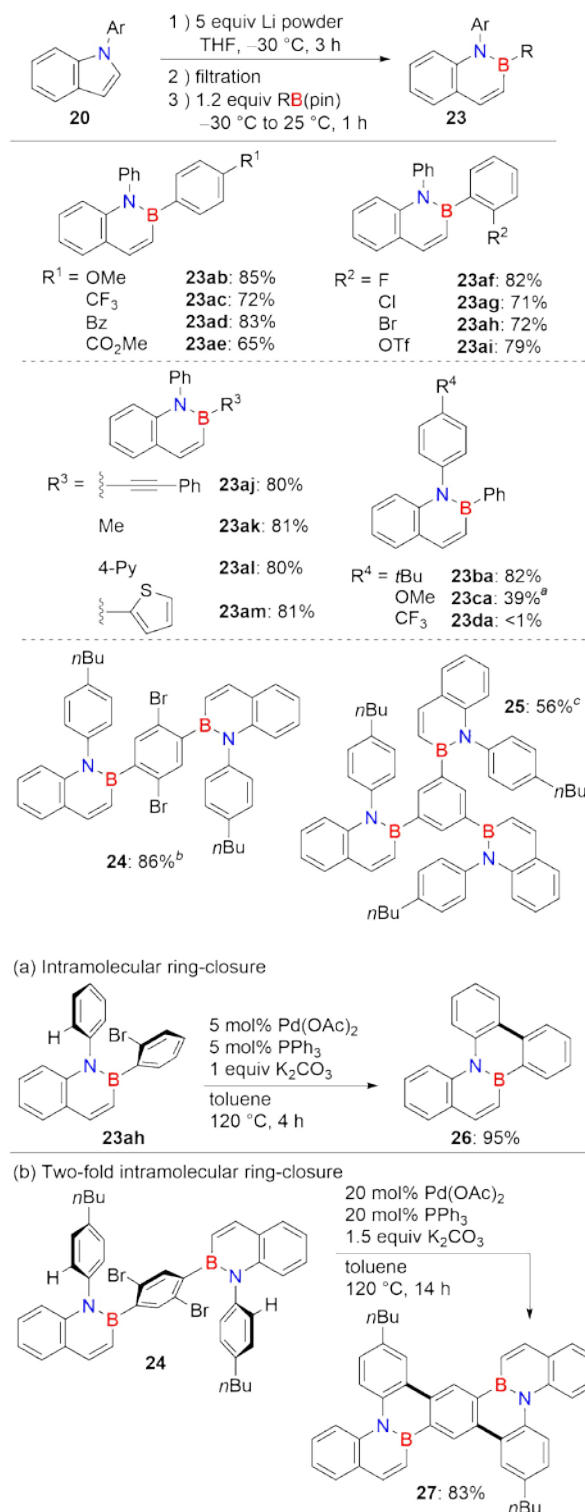
A wide range of arylboronates could be used as boron sources for this azaborin synthesis with high compatibility of functional groups (Table 8). Surprisingly, carbonyl groups and halogen atoms endured the reaction conditions although organolithium species existed in the reaction mixture (**23ae–23ai**). Alkyl-, alkynyl-, and heteroarylboronates were also applicable (**23aj–23am**). While a variety of boronates could be used, neither electron donating or withdrawing groups at the phenyl ring on the nitrogen atom retarded the reaction (**23ca** and **23da**). This boron insertion of indoles could construct complicated polyarenes bearing multiple azaborin units by employing the corresponding di- and triboronic acid esters as electrophiles (**24**, **25**).

Due to the good compatibility of functional groups on arylboronates with the reaction conditions, this boron insertion into indoles could provide ideal precursors of BN analogues of polyaromatic hydrocarbons.³³ Azaborin **23ah** from a bromo-substituted arylboronate successfully underwent intramolecular ring-closure with the aid of a palladium catalyst and a base (Scheme 16). In a similar manner, two-fold ring-closure of **24** successfully proceeded to form **27**.

Conclusion

This Highlight Review briefly summarizes skeletal transformations of benzofurans and indoles with breaking their aromatic cores. As shown above, those two heteroarenes have obtained new roles of synthetic building blocks for other heterocycles, and the concept of “aromatic metamorphosis” has been growing as a reliable synthetic methodology to provide novel and valuable molecules. Further progress in this field will disclose new chemical space for both synthetic and material chemistry.

Table 8. Reaction scope of boron insertion into indoles. ^a2 equiv of PhB(pin) was used. ^b0.5 equiv of the corresponding arylboronate was used. ^c0.2 equiv of the corresponding arylboronate was used.



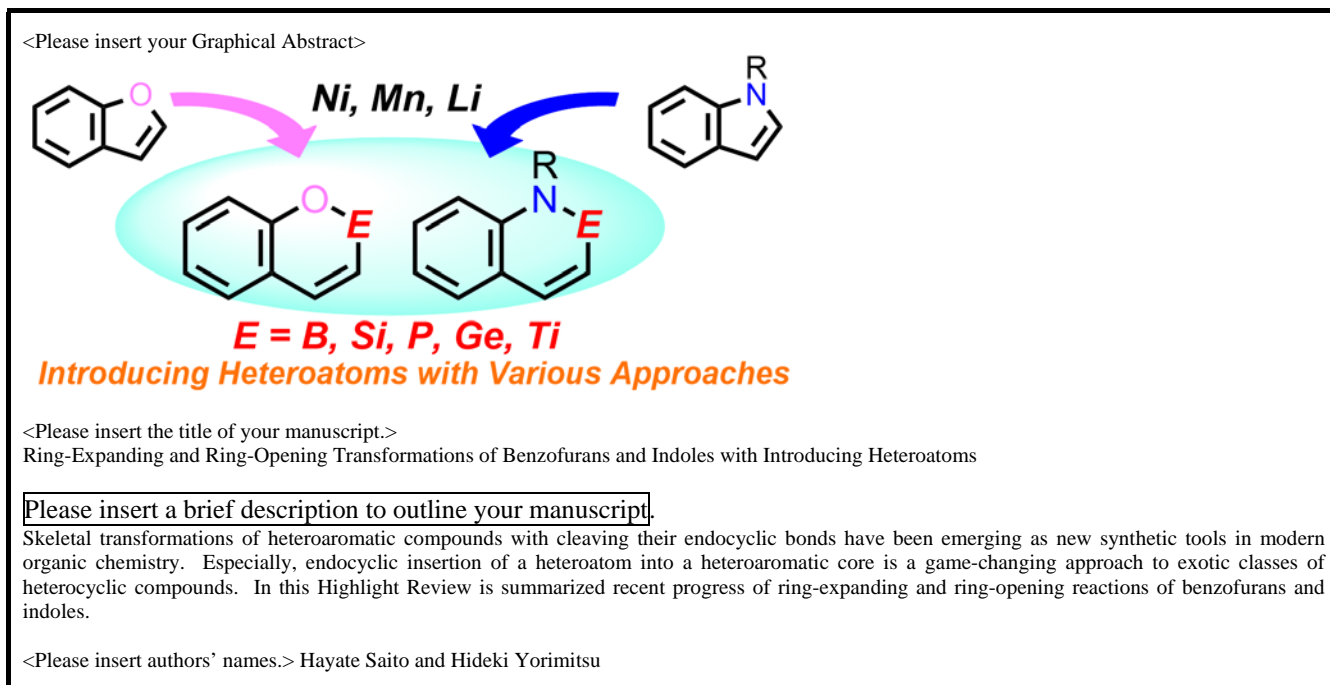
Scheme 16. Intramolecular ring-closure of azaborins **23ah** and **24**.

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